

INTERNATIONAL COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference X-13161	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 00/ 06418	International filing date (day/month/year) 20/03/2000	(Earliest) Priority Date (day/month/year) 30/03/1999
Applicant ELI LILLY AND COMPANY et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :
- ☒ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of Invention is lacking** (see Box II).

4. With regard to the title,

- ☒ the text is approved as submitted by the applicant.
- ☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

- ☒ the text is approved as submitted by the applicant.
- ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

- ☒ as suggested by the applicant.
- ☐ because the applicant failed to suggest a figure.
- ☐ because this figure better characterizes the invention.

1
☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

US 00/06418

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/12 C07K14/705 C12P21/02 A61K38/17 A61P11/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07K C12P A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

STRAND, EMBL, EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 30694 A (HUMAN GENOME SCIENCES INC ;FENG PING (US); NI JIAN (US); EBNER REI) 16 July 1998 (1998-07-16) page 4, line 8-27 page 9, line 3-11 page 22, line 26 -page 29, line 9 page 33, line 5-17 example 3A figure 3 ---	19
X	WO 99 14330 A (GENENTECH INC) 25 March 1999 (1999-03-25) page 8, line 31-42 page 15, line 43 -page 16, line 36 figure 4; example 1 examples 7,9 --- -/--	19

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

19 September 2000

Date of mailing of the international search report

29/09/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

van de Kamp, M

INTERNATIONAL SEARCH REPORT

International Application No

US 00/06418

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PITTI ET AL: "Genomic amplification of a decoy receptor for FAS ligand in lung and colon cancer" NATURE, vol. 396, 17 December 1998 (1998-12-17), pages 699-703, XP002139977 abstract ---	
P,X	WO 99 50413 A (MIZRAHI JACQUES ;HEUER JOSEF GEORG (US); NOBLITT TIMOTHY WAYNE (US) 7 October 1999 (1999-10-07) page 11, line 25 -page 12, line 10 examples 6,10 figures 2,4 ---	1,4,8, 19,20, 24,31, 32,44, 46,48,49
T	SHEIKH M S ET AL.: "Death and decoy receptors and p53-mediated apoptosis" LEUKEMIA, vol. 14, no. 8, August 2000 (2000-08), pages 1509-1513, XP000946082 abstract -----	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

US 00/06418

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9830694	A	16-07-1998	AU 5815798 A	03-08-1998
			AU 6238698 A	03-08-1998
			BR 9806954 A	21-03-2000
			CN 1247567 T	15-03-2000
			EP 1007659 A	14-06-2000
			EP 0990031 A	05-04-2000
			WO 9830693 A	16-07-1998
WO 9914330	A	25-03-1999	AU 9497098 A	05-04-1999
			EP 1015587 A	05-07-2000
WO 9950413	A	07-10-1999	AU 3369199 A	18-10-1999
			WO 0037094 A	29-06-2000

PATENT COOPERATION TREATY

RECEIVED RECEIVED

JUN 15 2001

JUN 15 2001

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

ELI LILLY & COMPANY
PATENT DIVISION

To:

WEBSTER, Thomas D.
ELI LILLY AND COMPANY
Lilly Corporate Center
Indianapolis, Indiana 46285
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing
(day/month/year) 06.06.2001

Applicant's or agent's file reference
X-13161

IMPORTANT NOTIFICATION

International application No.
PCT/US00/06418

International filing date (day/month/year)
20/03/2000

Priority date (day/month/year)
30/03/1999

Applicant
ELI LILLY AND COMPANY et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

 European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer

CLEERE, C

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference X-13161	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US00/06418	International filing date (day/month/year) 20/03/2000	Priority date (day/month/year) 30/03/1999
International Patent Classification (IPC) or national classification and IPC C12N15/12		
Applicant ELI LILLY AND COMPANY et al.		
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 7 sheets.</p>		
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input checked="" type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input checked="" type="checkbox"/> Certain observations on the international application 		
Date of submission of the demand 10/10/2000	Date of completion of this report 06.06.2001	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Trommsdorff, M Telephone No. +49 89 2399 7361	



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US00/06418

I. Basis of the report

1. With regard to the elements of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17):*

Description, pages:

1-74 as originally filed

Claims, No.:

1-23 as received on 25/04/2001 with letter of 25/04/2001

Drawings, sheets:

1/7-7/7 as originally filed

Sequence listing part of the description, pages:

1-5, filed with the letter of 15.06.00

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
 - ☐ the language of publication of the international application (under Rule 48.3(b)).
 - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).
3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:
- ☐ contained in the international application in written form.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority in written form.
 - ☒ furnished subsequently to this Authority in computer readable form.
 - ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
 - ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.
4. The amendments have resulted in the cancellation of:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US00/06418

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-18, 20, 21
	No:	Claims	19, 22, 23
Inventive step (IS)	Yes:	Claims	1-18, 20, 21
	No:	Claims	19, 22, 23
Industrial applicability (IA)	Yes:	Claims	1-13, 16, 17, 19-23
	No:	Claims	14, 15, 18: no opinion

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/06418

1. Cited documents

The following documents (D) are referred to in this communication; the numbering is the same as in the search report and will be adhered to in the rest of the procedure:

- D1: WO 98 30694 A (HUMAN GENOME SCIENCES INC ;FENG PING (US); NI JIAN (US); EBNER REI) 16 July 1998 (1998-07-16)
- D2: WO 99 14330 A (GENENTECH INC) 25 March 1999 (1999-03-25)
- D3: PITTI ET AL: 'Genomic amplification of a decoy receptor for FAS ligand in lung and colon cancer' NATURE, vol. 396, 17 December 1998 (1998-12-17), p. 699-703,
- D4: WO 99 50413 A (MIZRAHI JACQUES ;HEUER JOSEF GEORG (US); NOBLITT TIMOTHY WAYNE (US) 7 October 1999 (1999-10-07)

2. Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The present application describes a tumor necrosis factor receptor protein (TNFR) homologue, namely Fas Ligand Inhibitory Protein (FLINT) and more specifically protease resistant mutants of FLINT. FLINT binds Fas Ligand (FasL) and thereby prevents the interaction between FasL and Fas. The Fas-FasL signal transduction pathway is known to be involved in a number of diseases. According to the applicants, when FLINT undergoes proteolysis, the resulting FLINT metabolite seems to bind FasL with a lower affinity than FLINT. The applicants thus claim FLINT mutants which are resistant to protease by mutation at or near amino acid position 218.

- 2.1. D1, D2 and D3 disclose sequences of TNFR homologues: D1 gives the sequence of two splice variants TNFR-6 α and TNRF-6 β . D2 and D3 describe the identification of DcR3. The sequence alignment shows a 100% identity between the sequences of said homologues and FLINT. Thus, FLINT was known from the prior art.

Although D1 and D2 claim said TNFR homologues and derivatives, neither D1 nor

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/06418

D2 mention the fact that FLINT undergoes proteolysis and that the proteolytic site is at amino acid position 218.

Since protease resistant FLINT analogues are not disclosed or suggested by the prior art, the subject-matter of claims 1-13, 16, 17, 20 and 21 is novel and inventive with the restrictions made in § 4 below (Art. 33(1)-(3) PCT).

Consequently, claims 14, 15 and 18 directed to methods of treatment using said protease resistant FLINT analogues are also novel and inventive (Art. 33(1)-(3) PCT).

- 2.2. Claim 19 is directed to a FLINT analog which is at least 50% identical with residues 214 through 222 of seq. ID no. 1. Due to the broad scope embraced by said claim, any given molecule which shares at least 5 identical amino acids with seq. ID no. 1 between aa 214-222 and which is protease resistant. It is therefore impossible to assess which are exactly the molecules embraced by said claim. Moreover, due to the broad scope of said claim, there is no doubt than known molecules will fall into the scope of said claim (Art. 33(1) and (2) PCT).
- 2.3. Claims 22 and 23 are directed to vectors and host cells comprising "a nucleic acid of the present invention". Said vague expression renders the scope of said claims so broad that the molecules disclosed in D1-D3 are prejudicial to the novelty of said claims.
- 2.4. Claims 14, 15 and 18 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(i) PCT).

3. Re Item VI

Certain documents cited

The priority of the present application has not been checked and thus, document D4 cited below will not be considered as part of the prior art for the time being. However, if the priority was not valid for part of the claims, D4 could be prejudicial to the novelty of said claims. Furthermore, D4 has an earlier priority date as the present application and could thus be prejudicial to the novelty of all claims at a

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/06418

later stage of examination. Note that D4 discloses FLINT variants having a Gly214 to Ala substitution (Figs. 2 and 4).

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
PCT/US99/06797	07.10.99	30.03.99	30.03.98

4. Re Item VIII

Certain observations on the international application

- 4.1. The applicants claim protease resistant analogs of FLINT. On page 3 of the description, the applicants state that the FLINT metabolite (product of proteolysis) is less efficient in binding FasL than FLINT and that therefore the claimed protease resistant analogs could enhance the pharmaceutical utility of FLINT. However, a document reflecting said assumptions is not identified in the description (Rule 5.1(a)(ii) PCT). Since the sequence of FLINT and the use of said molecule and of analogs for therapeutic goals has already been disclosed in D1 and D2, the claimed FLINT analogs can only be considered as inventive over D1 and D2 if the claimed "special effect", i.e. an enhanced pharmaceutical utility compared to the native FLINT, is shown by the applicants. If this is not the case, said analogs merely represent an arbitrary selection of the possible mutants and are not inventive.

This question becomes even more relevant in the light of example 6 describing *in vitro* experiments comparing the effect of FLINT and FLINT analogs on apoptosis. The results on page 61 show that most of the FLINT analogs are less efficient than the native FLINT in inhibiting apoptosis. Example 11 shows an *in vivo* experiment, wherein mice with liver damage are treated with FLINT or FLINT analogs. Here again, the survival rate of the mice treated with FLINT is higher. Thus, in the light of the description, it remains questionable if said FLINT analogs really have an enhanced pharmaceutical utility compared to FLINT and thus if the subject-matter claimed is inventive.

- 4.2. Furthermore, the claims are not fully supported by the description for the following reasons (Art. 6 PCT):
Although the claims embrace a multitude of protease resistant FLINT analogs, i.e.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/06418

molecules that do not even necessarily share a high homology to seq. ID no. 1, the resistance of said molecules to proteolysis is only shown for one specific mutant containing seq. ID no. 1 with only one mutation at position 218 (see examples 13 and 14). It is highly unlikely that all the mutations claimed will lead to protease resistant molecules. Moreover, said claimed molecules should also present a similar activity than the native FLINT (effect on apoptosis, etc.) It would represent an undue burden for the skilled person trying to find out which of the numerous possible molecules will indeed be resistant to proteolysis and act as inhibitors of apoptosis like FLINT. Consequently, the scope of the claims is too broad and needs to be restricted accordingly.

P/ NT COOPERATION TREAT

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
 US Department of Commerce
 United States Patent and Trademark
 Office, PCT
 2011 South Clark Place Room
 CP2/5C24
 Arlington, VA 22202
 ETATS-UNIS D'AMERIQUE
 in its capacity as elected Office

Date of mailing (day/month/year) 03 November 2000 (03.11.00)	
International application No. PCT/US00/06418	Applicant's or agent's file reference X-13161
International filing date (day/month/year) 20 March 2000 (20.03.00)	Priority date (day/month/year) 30 March 1999 (30.03.99)
Applicant MICANOVIC, Radmila et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

10 October 2000 (10.10.00)

☐ in a notice effecting later election filed with the International Bureau on:
2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Nestor Santesso Telephone No.: (41-22) 338.83.38
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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
5 October 2000 (05.10.2000)

PCT

(10) International Publication Number
WO 00/58466 A3

(51) International Patent Classification⁷: **C12N 15/12**,
C07K 14/705, **C12P 21/02**, **A61K 38/17**, **A61P 11/00**

(21) International Application Number: **PCT/US00/06418**

(22) International Filing Date: **20 March 2000 (20.03.2000)**

(25) Filing Language: **English**

(26) Publication Language: **English**

(30) Priority Data:

60/126,839	30 March 1999 (30.03.1999)	US
60/140,073	21 June 1999 (21.06.1999)	US
60/147,071	4 August 1999 (04.08.1999)	US
60/160,524	20 October 1999 (20.10.1999)	US
60/160,669	21 October 1999 (21.10.1999)	US
60/172,744	20 December 1999 (20.12.1999)	US
60/178,184	26 January 2000 (26.01.2000)	US

Radmila [US/US]; 7126 White Oak Trail, Indianapolis, IN 46236 (US). **RATHNACHALAM**, Radhakrishnan [IN/US]; 3793 Lattice Court, Carmel, IN 46032 (US). **WITCHER**, Derrick, Ryan [US/US]; 10896 Parrot Court, Fishers, IN 46038 (US).

(74) Agents: **WEBSTER**, Thomas, D. et al.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).

(81) Designated States (*national*): AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(71) Applicant (*for all designated States except US*): **ELI LILLY AND COMPANY** [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).

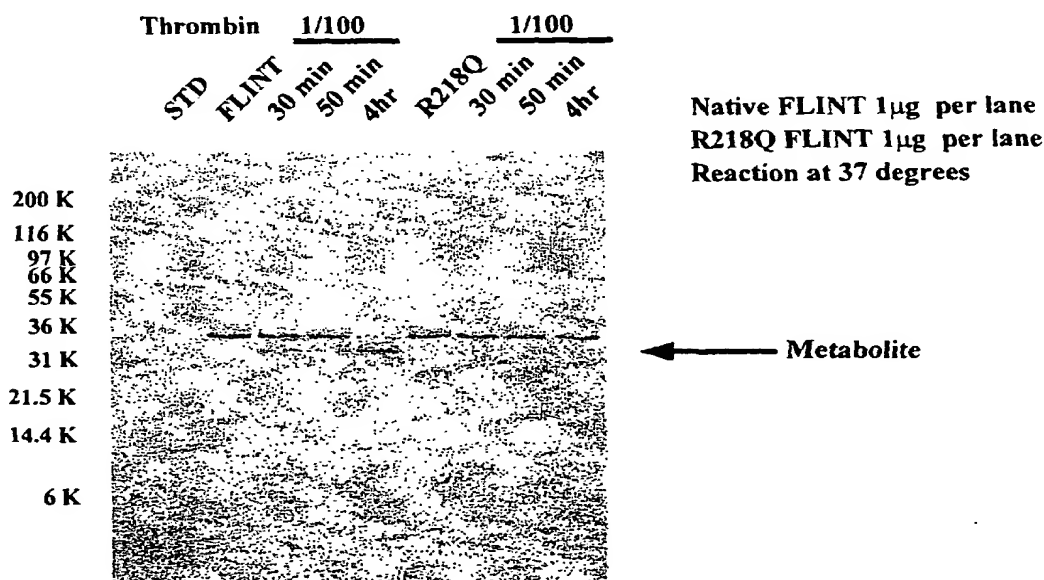
(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **MICANOVIC**,

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: **PROTEASE RESISTANT FLINT ANALOGS**



(57) Abstract: The invention relates to FLINT analogs that are resistant to proteolysis *in vivo* and *in vitro* at amino acid position 218 of mature FLINT, clinical and therapeutic uses thereof, and pharmaceutical formulations comprising said analogs.

WO 00/58466 A3

WO 00/58466 A3



Published:

— *With international search report.*

(88) Date of publication of the international search report:

11 January 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/06418

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/12 C07K14/705 C12P21/02 A61K38/17 A61P11/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07K C12P A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

STRAND, EMBL, EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 30694 A (HUMAN GENOME SCIENCES INC ;FENG PING (US); NI JIAN (US); EBNER REI) 16 July 1998 (1998-07-16) page 4, line 8-27 page 9, line 3-11 page 22, line 26 -page 29, line 9 page 33, line 5-17 example 3A figure 3	19
X	WO 99 14330 A (GENENTECH INC) 25 March 1999 (1999-03-25) page 8, line 31-42 page 15, line 43 -page 16, line 36 figure 4; example 1 examples 7,9	19
	-/-	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

19 September 2000

Date of mailing of the international search report

29/09/2000

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

In International Application No

PCT/US 00/06418

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